

DISULFIRAM- disulfiram tablet
Sigmapharm Laboratories, LLC

Disulfiram Tablets, USP

IN ALCOHOLISM

WARNING:

Disulfiram should *never* be administered to a patient when he is in a state of alcohol intoxication, or without his full knowledge. The physician should instruct relatives accordingly.

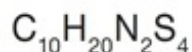
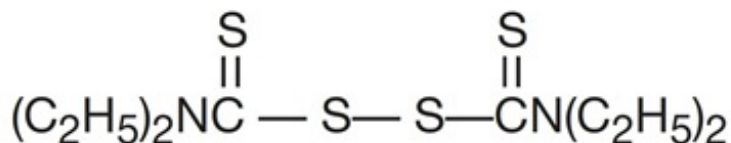
DESCRIPTION:

Disulfiram is an alcohol antagonist drug.

CHEMICAL NAME:

bis(diethylthiocarbamoyl) disulfide.

STRUCTURAL FORMULA:



M.W. 296.54

Disulfiram occurs as a white to off-white, odorless, and almost tasteless powder, soluble in water to the extent of about 20 mg in 100 mL, and in alcohol to the extent of about 3.8 g in 100 mL.

Each tablet for oral administration contains 250 mg or 500 mg disulfiram, USP. Tablets also contain crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and silicon dioxide.

CLINICAL PHARMACOLOGY:

Disulfiram produces a sensitivity to alcohol which results in a highly unpleasant reaction when the patient under treatment ingests even small amounts of alcohol.

Disulfiram blocks the oxidation of alcohol at the acetaldehyde stage. During alcohol metabolism following disulfiram intake, the concentration of acetaldehyde occurring in the blood may be 5 to 10 times higher than that found during metabolism of the same amount of alcohol alone.

Accumulation of acetaldehyde in the blood produces a complex of highly unpleasant symptoms referred to hereinafter as the disulfiram-alcohol reaction. This reaction, which is proportional to the dosage of both disulfiram and alcohol, will persist as long as alcohol is being metabolized. Disulfiram does not appear to influence the rate of alcohol elimination from the body.

Disulfiram is absorbed slowly from the gastrointestinal tract and is eliminated slowly from the body. One (or even two) weeks after a patient has taken his last dose of disulfiram, ingestion of alcohol may produce unpleasant symptoms.

Prolonged administration of disulfiram does not produce tolerance; the longer a patient remains on therapy, the more exquisitely sensitive he becomes to alcohol.

INDICATIONS AND USAGE:

Disulfiram is an aid in the management of selected chronic alcohol patients who *want* to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage.

Disulfiram is not a cure for alcoholism. When used alone, without proper motivation and supportive therapy, it is unlikely that it will have any substantive effect on the drinking pattern of the chronic alcoholic.

CONTRAINDICATIONS:

Patients who are receiving or have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing preparations, e.g., cough syrups, tonics and the like, should not be given disulfiram.

Disulfiram is contraindicated in the presence of severe myocardial disease or coronary occlusion, psychoses, and hypersensitivity to disulfiram or to other thiuram derivatives used in pesticides and rubber vulcanization.

WARNINGS:

Disulfiram should *never* be administered to a patient when he is in a state of alcohol intoxication, or without his full knowledge. The physician should instruct relatives accordingly.

The patient must be fully informed of the disulfiram-alcohol reaction. He must be strongly cautioned against surreptitious drinking while taking the drug, and he must be fully aware of the possible consequences. He should be warned to avoid alcohol in disguised forms, i.e., in sauces, vinegars, cough mixtures, and even in aftershave lotions and back rubs. He should also be warned that reactions may occur with alcohol

up to 14 days after ingesting disulfiram.

The Disulfiram-Alcohol Reaction:

Disulfiram plus alcohol, even small amounts, produce flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death.

The intensity of the reaction varies with each individual, but is generally proportional to the amounts of disulfiram and alcohol ingested. Mild reactions may occur in the sensitive individual when the blood alcohol concentration is increased to as little as 5 to 10 mg per 100 mL. Symptoms are fully developed at 50 mg per 100 mL, and unconsciousness usually results when the blood alcohol level reaches 125 to 150 mg.

The duration of the reaction varies from 30 to 60 minutes, to several hours in the more severe cases, or as long as there is alcohol in the blood.

Concomitant Conditions:

Because of the possibility of an accidental disulfiram-alcohol reaction, disulfiram should be used with extreme caution in patients with any of the following conditions: diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis, hepatic cirrhosis or insufficiency.

PRECAUTIONS:

Patients with a history of rubber contact dermatitis should be evaluated for hypersensitivity to thiuram derivatives before receiving disulfiram (see CONTRAINDICATIONS).

It is suggested that every patient under treatment carry an *Identification Card* stating that he is receiving disulfiram and describing the symptoms most likely to occur as a result of the disulfiram-alcohol reaction. In addition, this card should indicate the physician or institution to be contacted in an emergency. (Cards may be obtained from Sigmapharm Laboratories, LLC. upon request.)

Alcoholism may accompany or be followed by dependence on narcotics or sedatives. Barbiturates and disulfiram have been administered concurrently without untoward effects; the possibility of initiating a new abuse should be considered.

Hepatic toxicity including hepatic failure resulting in transplantation or death have been reported. Severe and sometimes fatal hepatitis associated with disulfiram therapy may develop even after many months of therapy. Hepatic toxicity has occurred in patients with or without prior history of abnormal liver function. Patients should be advised to immediately notify their physician of any early symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, vomiting, jaundice, or dark urine.

Baseline and follow-up liver function tests (10-14 days) are suggested to detect any hepatic dysfunction that may result with disulfiram therapy. In addition, a complete

blood count and serum chemistries, including liver function tests, should be monitored.

Patients taking disulfiram tablets should not be exposed to ethylene dibromide or its vapors. This precaution is based on preliminary results of animal research currently in progress that suggest a toxic interaction between inhaled ethylene dibromide and ingested disulfiram resulting in a higher incidence of tumors and mortality in rats. A correlation between this finding and humans, however, has not been demonstrated.

Drug Interactions:

Disulfiram appears to decrease the rate at which certain drugs are metabolized and therefore may increase the blood levels and the possibility of clinical toxicity of drugs given concomitantly.

DISULFIRAM SHOULD BE USED WITH CAUTION IN THOSE PATIENTS RECEIVING PHENYTOIN AND ITS CONGENERS, SINCE THE CONCOMITANT ADMINISTRATION OF THESE TWO DRUGS CAN LEAD TO PHENYTOIN INTOXICATION. PRIOR TO ADMINISTERING DISULFIRAM TO A PATIENT ON PHENYTOIN THERAPY, A BASELINE PHENYTOIN SERUM LEVEL SHOULD BE OBTAINED. SUBSEQUENT TO INITIATION OF DISULFIRAM THERAPY, SERUM LEVELS OF PHENYTOIN SHOULD BE DETERMINED ON DIFFERENT DAYS FOR EVIDENCE OF AN INCREASE OR FOR A CONTINUING RISE IN LEVELS. INCREASED PHENYTOIN LEVELS SHOULD BE TREATED WITH APPROPRIATE DOSAGE ADJUSTMENT.

It may be necessary to adjust the dosage of oral anticoagulants upon beginning or stopping disulfiram, since disulfiram may prolong prothrombin time.

Patients taking isoniazid when disulfiram is given should be observed for the appearance of unsteady gait or marked changes in mental status, the disulfiram should be discontinued if such signs appear.

In rats, simultaneous ingestion of disulfiram and nitrite in the diet for 78 weeks has been reported to cause tumors, and it has been suggested that disulfiram may react with nitrites in the rat stomach to form a nitrosamine, which is tumorigenic. Disulfiram alone in the rat's diet did not lead to such tumors. The relevance of this finding to humans is not known at this time.

Usage in Pregnancy:

The safe use of this drug in pregnancy has not been established. Therefore, disulfiram should be used during pregnancy only when, in the judgment of the physician, the probable benefits outweigh the possible risks.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Since many drugs are so excreted, disulfiram should not be given to nursing mothers.

Geriatric Use:

A determination has not been made whether controlled clinical studies of disulfiram

included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:

(See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS.)

OPTIC NEURITIS, PERIPHERAL NEURITIS, POLYNEURITIS, AND PERIPHERAL NEUROPATHY MAY OCCUR FOLLOWING ADMINISTRATION OF DISULFIRAM.

Multiple cases of hepatitis, including both cholestatic and fulminant hepatitis, as well as hepatic failure resulting in transplantation or death, have been reported with administration of disulfiram.

Occasional skin eruptions are, as a rule, readily controlled by concomitant administration of an antihistaminic drug.

In a small number of patients, a transient mild drowsiness, fatigability, impotence, headache, acneform eruptions, allergic dermatitis, or a metallic or garlic-like aftertaste may be experienced during the first two weeks of therapy. These complaints usually disappear spontaneously with the continuation of therapy, or with reduced dosage.

Psychotic reactions have been noted, attributable in most cases to high dosage, combined toxicity (with metronidazole or isoniazid), or to the unmasking of underlying psychoses in patients stressed by the withdrawal of alcohol.

To report **SUSPECTED ADVERSE REACTIONS**, contact Sigmapharm Laboratories, LLC, Pharmacovigilance at 1-855-332-0731 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE:

No specific information is available on the treatment of overdosage with disulfiram. It is recommended that the physician contact the local Poison Control Center.

DOSAGE AND ADMINISTRATION:

Disulfiram should never be administered until the patient has abstained from alcohol for at least 12 hours.

Initial Dosage Schedule:

In the first phase of treatment, a *maximum* of 500 mg daily is given in a single dose for one to two weeks. Although usually taken in the morning, disulfiram may be taken on retiring by patients who experience a sedative effect. Alternatively, to minimize, or eliminate, the sedative effect, dosage may be adjusted downward.

Maintenance Regimen:

The average maintenance dose is 250 mg daily (range, 125 to 500 mg), it should not exceed 500 mg daily.

Note: Occasionally patients, while seemingly on adequate maintenance doses of disulfiram, report that they are able to drink alcoholic beverages with impunity and without any symptomatology. All appearances to the contrary, such patients must be presumed to be disposing of their tablets in some manner without actually taking them. Until such patients have been observed reliably taking their daily disulfiram tablets (preferably crushed and well mixed with liquid), it cannot be concluded that disulfiram is ineffective.

Duration of Therapy:

The daily, uninterrupted administration of disulfiram must be continued until the patient is fully recovered socially and a basis for permanent self-control is established. Depending on the individual patient, maintenance therapy may be required for months or even years.

Trial with Alcohol:

During early experience with disulfiram, it was thought advisable for each patient to have at least one supervised alcohol-drug reaction. More recently, the test reaction has been largely abandoned. Furthermore, such a test reaction should never be administered to a patient over 50 years of age. A clear, detailed and convincing description of the reaction is felt to be sufficient in most cases.

However, where a test reaction is deemed necessary, the suggested procedure is as follows:

After the first one to two weeks' therapy with 500 mg daily, a drink of 15 mL (1/2 oz) of 100 proof whiskey, or equivalent, is taken slowly. This test dose of alcoholic beverage may be repeated once only, so that the total dose does not exceed 30 mL (1 oz) of whiskey. Once a reaction develops, no more alcohol should be consumed. Such tests should be carried out only when the patient is hospitalized, or comparable supervision and facilities, including oxygen, are available.

Management of Disulfiram-Alcohol Reaction:

In severe reactions, whether caused by an excessive test dose or by the patient's unsupervised ingestion of alcohol, supportive measures to restore blood pressure and treat shock should be instituted. Other recommendations include: oxygen, carbogen (95% oxygen and 5% carbon dioxide), vitamin C intravenously in massive doses (1 g) and ephedrine sulfate. Antihistamines have also been used intravenously. Potassium levels should be monitored, particularly in patients on digitalis, since hypokalemia has been reported.

HOW SUPPLIED:

Disulfiram Tablets, USP:

250 mg - White, capsule shaped tablets debossed "Σ 28" on one side and plain on the other side. They are available in bottles of 30's (NDC 42794-028-08).

500 mg - White, capsule shaped bisected tablets debossed with “Σ” and “29” on either side of the bisection and plain on the other side. They are available in bottles of 30’s (NDC 42794-029-08).

Dispense in original container. Do not remove desiccant and adsorbent canisters from the bottle.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

Manufactured by:

Sigmapharm Laboratories, LLC
Bensalem, PA 19020

OS029A-01 REV.0321

Disulfiram 250 mg Container Label

NDC 42794-028-08

Disulfiram Tablets, USP

250 mg

PHARMACIST: DISPENSE IN THE ORIGINAL CONTAINER. SEE SIDE PANEL FOR WARNINGS.

Rx Only

30 Tablets

NDC 42794-028-08

**Disulfiram
Tablets, USP**

250 mg

PHARMACIST: DISPENSE IN THE ORIGINAL CONTAINER. SEE SIDE PANEL FOR WARNINGS


SigmaPharm
LABORATORIES

Rx only
30 Tablets

Each Tablet Contains:
Disulfiram, USP 250 mg

Usual Dosage: See package insert.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Dispense in original container. Do not remove desiccant and adsorbent canisters from the bottle.

WARNING: To The Physician: This is a potent drug; indiscriminate use may result in serious undesirable reactions. Before administering this product, physicians should familiarize themselves with the enclosed literature.

To The Pharmacist: When dispensing this product include the following as part of the Rx labeling:

WARNING: Administration of this drug without the full knowledge of the patient may result in serious complications.

SigmaPharm Laboratories, LLC
Bensalem, PA 19020


N 42794 02808 3

L142.00-R1019

Disulfiram 500 mg Container Label

NDC 42794-029-08

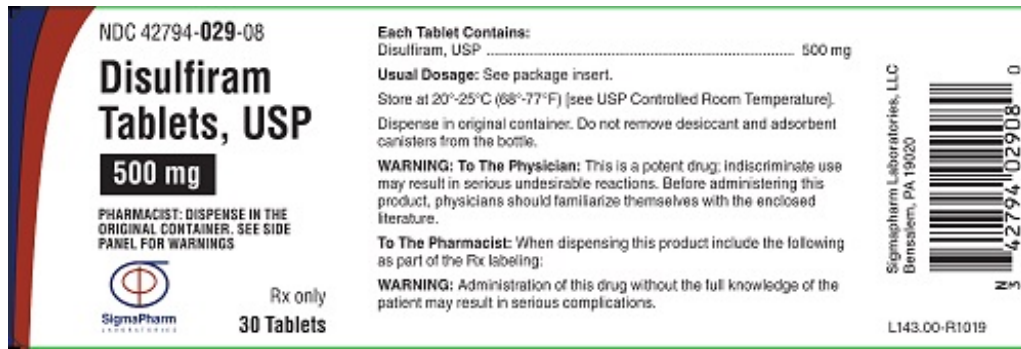
Disulfiram Tablets, USP

500 mg

PHARMACIST: DISPENSE IN THE ORIGINAL CONTAINER. SEE SIDE PANEL FOR WARNINGS.

Rx Only

30 Tablets



DISULFIRAM

disulfiram tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:42794-028
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DISULFIRAM (UNII: TR3MLJ1UAI) (DISULFIRAM - UNII:TR3MLJ1UAI)	DISULFIRAM	250 mg

Inactive Ingredients

Ingredient Name	Strength
CROSPROVIDONE (UNII: 2S7830E561)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	white (white to off-white)	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	28
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42794-028-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/01/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091619	11/01/2021	

DISULFIRAM

disulfiram tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:42794-029
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DISULFIRAM (UNII: TR3MLJ1UAI) (DISULFIRAM - UNII:TR3MLJ1UAI)	DISULFIRAM	500 mg

Inactive Ingredients

Ingredient Name	Strength
CROSPROVIDONE (UNII: 2S7830E561)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	white (white to off-white)	Score	2 pieces
Shape	CAPSULE	Size	19mm
Flavor		Imprint Code	29
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42794-029-08	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/11/2022	01/11/2022

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
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ANDA	ANDA091619	01/11/2022	01/11/2022
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Labeler - Sigmapharm Laboratories, LLC (556234636)

Registrant - Sigmapharm Laboratories, LLC (556234636)

Establishment

Name	Address	ID/FEI	Business Operations
Sigmapharm Laboratories, LLC		556234636	manufacture(42794-028, 42794-029) , analysis(42794-028, 42794-029)

Revised: 1/2022

Sigmapharm Laboratories, LLC